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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SHIBUYA, MARK LANCE

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 02/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/667,237	REINL ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *5-8,16-48 and 51* is/are withdrawn from consideration.

5)☒ Claim(s) *49 and 50* is/are allowed.

6)☒ Claim(s) *1-4 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-51 are pending. Claims 16-48 and 51 are withdrawn from consideration as drawn to a non-elected Invention and Claims 5-8 are withdrawn from consideration as drawn to a non-elected species, (*i.e.*, claims 5-8, 16-48 and 51 are withdrawn). Claim 50 is rejoined. Claims 1-4, 9-15, 49 and 50 are examined.

Election/Restrictions

2. In regard to dependent claim 50, withdrawn from consideration as drawn to a non-elected invention, the examiner required restriction between the elected product (claim 49) and process of making claims (claim 50). Product claim 49 now is found allowable. Therefore the restriction between the product claim 49 and the process of claim 50 is withdrawn, and said process claim, which depends from the allowable product claim, is rejoined in accordance with the provisions of MPEP § 821.04. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. This application contains claims 16-48 and 51, drawn to an invention nonelected with traverse in Paper entered 4/30/2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Withdrawn Claim Rejections

4. The rejection of Claims 1-4, 9-15, and 49 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn, in part, in view of applicant's arguments and amendments to the claims, and upon further consideration. These amendments are to claim 1, line 1, inserting a comma after the term "molecules"; to claim 2, amended to read "wherein said repeated patter of degenerate repeated triplet nucleotides of said linkers has the following properties"; and to claim 49, line 1, inserting a comma after the term "molecules".

5. The rejection of Claim 49 under 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cwirla et al., Proc. Natl. Acad. Sci. USA, vol. 87, pp. 6378-6382, August 1990, is withdrawn after further consideration by the examiner, especially after reconsideration of the claim language stating "each of which has . . . the following properties", (claim 49, lines 3-4).

6. The rejection of Claim 49 under 35 U.S.C. 103(a) as being unpatentable over **Holliger et al.**, U.S. 5,837,242, **Keck et al.**, US 6,040,431, and **Dower et al.**, WO 91/19818, is withdrawn in view of applicant's arguments.

Priority

7. This application claims benefit of US Provision 60/155,978, filed 9/24/1999.

Information Disclosure Statement

8. The information disclosure statement, entered 1/23/2006, has been considered.

Maintained Claim Rejections - 35 USC § 112, Second Paragraph

9. Claims 1-4 and 9-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is maintained for the reasons of record as set forth in the previous Office action. The pertinent rejection is copied below for the convenience of the reader.

> The claims contain within them confusing antecedence and seemingly ungrammatical usage of verb tenses, which blur the claim limitations and their relationships to the claimed elements, and thereby render the claims vague and indefinite. For example, claim 1 recites the language "a linker which is a member of a randomized library of linkers that . . . (ii) consist of a repeated pattern . . .", which appears to be grammatically incorrect because the word "consist" is of the wrong tense.

Applicant argues that the subject of the term "consist" is "linkers", i.e., each of the linkers in the library consists of a repeated pattern of degenerate repeated triple nucleotides.

Response to Arguments

Applicant's arguments entered 1/23/2006 have been fully considered but they are not persuasive. Notwithstanding applicant's plausible explanation of the meaning of the claim, claim 1 remains vague and indefinite because it is not clear whether the subject is "linker" or "linkers". An amendment that might serve to make the claim clear, for example, could be:

--a linker which is a member of a randomized library of linkers, wherein the linkers (i) vary in size and nucleotide sequence--

However, as the claims currently stand, the claims may be interpreted with the subject as "linker".

Claim Rejections - 35 USC § 102/103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 1-4, 9, 12, 13 and 49 are rejected under 35 U.S.C. 102 (b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cwirla et al., Proc. Natl. Acad. Sci. USA, vol. 87, pp. 6378-6382, August 1990. This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

The claims are drawn to a library of dual-domain nucleic acid molecules each of which has (a) a first and a second domain; (b) separating and linking said domains, a linker which is a member of a randomized library of linkers that (i) vary in size and nucleotide sequence, (ii) consist of a repeated pattern of degenerate repeated triplet nucleotides, and variations thereof.

The claims are drawn to members of a randomized library of linkers that "consist of a repeated pattern of degenerate repeated triplet nucleotides." However, nucleic acid molecules, in and of themselves, do not have "degenerate" nucleotides. Thus the claims recite a limitation based upon the manner in which the linker library is made. As such, the claims are considered to claim products by process. The claims recite the connecting term "has", which is considered to be open claim language.

Cwirla et al., throughout the publication and abstract, and, e.g., at p. 6378, para 4, Figure 1, teach, for expression in phage, all possible hexapeptides with the sequence 5'-CTCT CAC TCC $(NNK)_6$ GGC GGC ACT GTT GAA AGT TGT-3', where N is A, C, G, or T and K is G or T, which reads on a library of dual-domain nucleic acid molecules, each of which comprises a first domain that is CTCT CAC TCC and a second domain that is GGC GGC ACT GTT GAA AGT TGT; and where $(NNK)_6$ is considered to read on a linker that separates and links said domains, and where $(NNK)_6$, considered to be a linker, can be a member of a randomized library of linkers that (i) vary in size and nucleotide sequence, and (ii) consist of a repeated pattern of degenerate repeated triplet nucleotides. Criwla et al., at e.g., p. 6382, para 2, teach generation of diversity by methods of degenerate synthesis of a codon, symbolized by the motif $(NNK)_6$. It would have been obvious, in the course of routine optimization of diversification, to have

further reduced K to a single nucleotide choice, such as T, thereby satisfying the limitations of claims 2 and 4.

Applicant argues that the publication of Cwirla et al. fails to disclose domains because a signal peptide is not a domain. Applicant points to p. 11 of the specification for the definition of a domain. Reply at p. 13, para 2. Applicant argues that Cwirla et al. does not teach a linker, as that limitation is used in the claims, or as defined in the specification at p. 14, lines 3-5. Applicant states: "[t]he term domain used in conjunction with polypeptides is defined on page 11 of the specification as 'a region of a polypeptide chain that is folded in such a way that confers a particular structure and/or biochemical function'", (Reply at p. 13, para 2). Applicant argues "[e]ven if the variable region of Cwirla could be considered a linker, which it cannot, the Cwirla variable region only varies in nucleotide sequence but not in length, as shown in Figure 4, on page 6381, for example." Applicant argues that Cwirla would not motivate one of ordinary skill in the art to vary a linker.

Response to Arguments

Applicant's arguments, entered 1/23/2006, have been fully considered but they are not persuasive.

The specification states: "A polypeptide or protein **"domain"** *generally* refers to a region of a polypeptide that is folded in such a way that confers a particular structure and/or biochemical function, [italics added]." Specification at p. 11, lines 28-30. Thus the specification does not provide a limiting definition for the term "domain".

Furthermore, the Reply does not provide objective evidence that a "signal peptide is not a domain", because no objective evidence is offered that the signal peptide taught by Cwirla et al., is not "folded in such a way that confers a particular structure and/or biochemical function." Absent objective evidence to the contrary, the signal peptide has a particular folded structure and a biochemical function related to transport or secretion. Without such objective the statement that a signal peptide is not a domain is merely attorney argument. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145.

Cwirla et al., at p. 6379, para 7, and Figure 1A, teach a "variable region" and spacer joining domains, thereby reading on a linker, and wherein the variable region comprises the nucleotide sequence $(NNK)_n$, where N can be any A, T, G or C and K is G or T. In Figure 4, Cwirla et al. teach hexapeptides, where **n** is six. Cwirla et al., at p. 6379, para 7, state "that the central portion contains one or more variable regions and also may code for spacer residues on either or both sides of the variable region." Thus Cwirla plainly teaches and suggests nucleotide sequences, reading on linkers, that vary in "size and nucleotide sequence", as in the instant claims. Therefore, the claims are properly rejected as anticipated by and obvious over the reference of Cwirla et al.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 1-4, 9, 12, 13 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Holliger et al.**, U.S. 5,837,242, **Keck et al.**, US 6,040,431, and **Dower et al.**, WO 91/19818. This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

The claims are drawn to a library of dual-domain nucleic acid molecules each of which has (a) a first and a second domain; (b) separating and linking said domains, a linker which is a member of a randomized library of linkers that (i) vary in size and nucleotide sequence, (ii) consist of a repeated pattern of degenerate repeated triplet nucleotides, and variations thereof.

The claims are drawn to members of a randomized library of linkers that "consist of a repeated pattern of degenerate repeated triplet nucleotides." However, nucleic acid molecules, in and of themselves, do not have "degenerate" nucleotides. Thus the claims recite a limitation based upon the manner in which the linker library is made. As such, the claims are considered to claim products by process. The claims recite the connecting term "has", which is considered to be open claim language.

Holliger et al., U.S. 5,837,242, throughout the patent, and at, e.g., col. 2-col. 3, teach dual domain dimers comprising binding regions of immunoglobulin variable regions linked by peptides of variable lengths, (so called "diabodies"), at col. 5-col. 6, nucleic acid sequences encoding such peptides, and at col. 26, teach phage display selection of diabodies, at col. 28-col. 29, bridging paragraph, construction of large combinatorial libraries of diabodies, at col. 8, lines 20-23, teach that alterations of the linker in the dimers can lead to an improvement in antigen binding affinity; at col. 54, lines 23-50, teach linkers of various lengths, and that the precise size of the linker that allows proper formation of the diabody is also likely to depend on the sequence of the linker, all of which read on libraries of dual domain nucleic acids, where linkers of various sizes and sequences separate and link the domains, as claimed.

Holliger does not teach explicitly libraries of linkers, and where the linkers of such a library are randomized, where the linkers consist of a "repeated pattern of degenerate repeated triplet nucleotides"; and where the random, "degenerate" coding sequence NNK, where N represents G, A, T and C and K represents T, is repeated (as in the instant dependent claims).

Keck et al., US 6,040,431, throughout the patent and at col. 3, lines 49-57, teach single chain constructs, termed morphons; at col. 4, teach domains, which are regions of TGF-beta superfamily proteins, that are linked by linkers and where the morphon constructions are assembled by joining DNA restriction fragments, at col. 5, teach that the linkers can be of variable lengths and are critical for maintaining the proper tertiary structure of the morphon, at col. 29-col. 30, teach a library of synthetic DNA constructs, that comprise a plurality of DNA molecules encoding different linker sequences encoding polypeptide linkers, and teach that if a plurality of DNA molecules encoding different linker sequences are included into a ligation reaction containing DNA molecules encoding TGF-beta domains, a library of DNA

constructs may be obtained, wherein each of the DNA constructs are connected by different linker sequences, thus reading on a library of linkers of varying sequences, as claimed.

Dower et al., WO 91/19818, throughout the publication, and at p. 2, line 30-p. 3, line 24, teach the construction of oligonucleotide libraries encoding peptides, and, e.g., at p. 4, lines 11-21, and p. 9, line 23-p. 10, line 11, teach generation of peptide diversity by the random, "degenerate" coding sequence $(NNK)_{5-8}$, where N represents G, A, T and C and K represents G and T; and teach that size of the library may become a constraint in the cloning process (see also, p. 11, lines 17-33).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used a library of dual-domain nucleic acid molecules comprising libraries of linkers, where the linkers of that library are randomized, where the linkers consist of a "repeated pattern of degenerate repeated triplet nucleotides", and where the random, "degenerate" coding sequence NNK, where N represents G, A, T and C and K represents T, is repeated.

One of ordinary skill in the art would have been motivated to have made and used dual-domain nucleic acid libraries, wherein the members of a library comprised a linker that was a member of a randomized library of linkers, because Keck et al. teach libraries of synthetic DNA constructs encoding different linker sequences, in order to select linkers capable of conferring the proper tertiary structure of multimers, and Keck teaches that choice of linker is critical for the proper spatial relationship of the linked domains.

One of ordinary skill in the art would have been motivated to have made and used randomized libraries of nucleic acid linker sequences that consist of a "repeated pattern of degenerate repeated triplet nucleotides", because Dower et al. teach a "repeated pattern of degenerate repeated triplet nucleotides", where the random, "degenerate" coding sequence NNK, wherein N represents G, A, T and C and K represents T and G, is repeated in order to generate a diversity of nucleic acids encoding a polypeptide.

One of ordinary skill the art would have been motivated to have made and used a nucleic acid with a repeating random, "degenerate" coding sequence NNK, wherein N represents G, A, T and C and K represents T, because Dower et al. teach a random, "degenerate" coding sequence NNK, where N represents G, A, T and C and K represents T and G, Dower teaches that increased size of a library is an important constraint in cloning process, so that it would be obvious that choosing to limit the value of K to T, as a part of routine optimization, in order to reduce the constraints of a large library, and because Dower already teaches reducing the choice of bases for K, as compared to N.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using a dual-domain nucleic acid library of nucleic acid molecules comprising libraries of linkers, where the linkers of that library are randomized, and where the linker consists of a "repeated pattern of degenerate repeated triplet nucleotides", and where the random, "degenerate" coding sequence NNK, wherein N represents G, A, T and C and K represents T, is repeated, because the use of linkers to connect multiple domains, linker libraries, and the generation of diversity of nucleic acids through repeats of random, degenerate triplet nucleotides, were all practiced in the art.

Applicant argues that because the cited references do not, together or separately, disclose all the limitations of claims 1-4, 9, 12 and 13, they do not render the claims obvious. The applicant states: "As the Examiner notes, however, the Hollinger patent does not disclose a randomized library of linkers that differ in both length and sequence, as set forth in claims 1-4, 9, 12 and 13", (Reply at p. 15, para 3). Applicant argues that the reference of Keck et al. teaches away from creating a randomized

library of linkers because Keck et al. "provides several *a priori* considerations for engineering such linker regions", (Reply at pp. 15-16, bridging paragraph). As an example, applicant points to col. 29-30, arguing that guidelines, such as avoiding cysteine residues, using a Gly_4Ser or Ser_4Gly repeat or using a computer algorithm to predict amino acid sequences that would be suitable to join heel and finger regions of a morphon peptide.

Applicant argues that Dower does not remedy the deficiencies of Keck and Holliger but that the variable coding regions taught by Dower, rather than encoding a variable linker region that joins two domains, encodes peptides of interest that are presented as ligands in a phage display system. Applicant argues that Dower teaches away from using this variable coding region as a linker for two peptides domains because Dower discloses joining two variable coding regions with a constant linker region that is pre-engineered to cause the peptides encoded by the variable coding region to be presented to the receptor in different ways. Applicant further argues that "in Dower's libraries of peptide ligands the variable region differs in sequence but not in length, as the variable x in $(NNK)_x$ or $(NNS)_x$ remains the same for each particular library."

Response to Arguments

Applicant's arguments, entered 1/23/2006, have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections

are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant states that "Keck does not suggest using a repeated pattern of degenerate repeated triplet nucleotides to obtain a randomized library of linkers that vary in sequence and length, as recited in Claim 1-4, 9, 12 and 13", (Reply at p. 16, para 1). However, the examiner respectfully submits that Keck et al., teach a library of synthetic DNA constructs, which comprise a plurality of DNA molecules encoding different linker sequences encoding polypeptide linkers, and wherein each of the DNA constructs are connected by different linker sequences, thus reading on a library of linkers of varying sequences, as claimed. Furthermore, Holliger et al. teach a plurality of linkers that are of variable lengths.

The examiner respectfully submits that Dower is cited for teaching the generation of peptide diversity by the random, "degenerate" coding sequence $(NNK)_{5-8}$, where N represents G, A, T and C and K represents G and T." As the cited prior art make plain, it was appreciated in the art at the time of the invention, that both the sequence and the length of the linkers used to connect protein domains, could affect the tertiary structure of the multimers and their binding of the domains to a target. Thus the references of Holliger et al., Keck et al., and Dower, disclose and suggest a randomized library of linkers that differ in both length and sequence, as set forth in claims 1-4, 9, 12 and 13.

12. Claims 10, 11, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Holliger et al.**, U.S. 5,837,242, **Keck et al.**, US 6,040,431, and **Dower et al.**, WO 91/19818, as applied to claims 1-4, 9, 12, 13 and 49 above, and **Turpen et al.**, WO 96/12028 (IDS filed 6/25/2002). This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

Claims 10, 11, 14 and 15 are drawn to dual-domain nucleic acid libraries, as, for example, in claim 1, and wherein the libraries and the individual molecules of the libraries, are produced in plant cells.

The references of **Holliger et al.**, U.S. 5,837,242, **Keck et al.**, US 6,040,431, and **Dower et al.**, WO 91/19818, are relied upon as in the above rejection under 35 USC 103.

The combined references of Holliger et al., U.S. 5,837,242, Keck et al., US 6,040,431, and Dower et al., WO 91/19818, taken as a whole, do not teach libraries and the individual molecules of the libraries, which are produced in plant cells.

Turpen et al., throughout the publication, and e.g., at p. 3, lines 7-30, pp. 4-5, bridging paragraph, teach using recombinant polynucleotides, comprised within plant viruses, in plant cells in order to produce large quantities of proteins of interest.

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used dual-domain nucleic acid libraries, as, for example, in claim 1, and wherein the libraries and the individual molecules of the libraries, are produced in plant cells.

One of ordinary skill in the art would have been motivated to have made and used dual-domain nucleic acid libraries in plant cells because Turpen teaches using plant viruses containing recombinant nucleic acids in order to achieve high levels of gene expression.

One of ordinary skill in the art would have had a reasonable expectation of success in producing dual-domain nucleic acid libraries in plant cells, because the genetic engineering of plant viruses, and the expression of those viruses in plant cells, were practiced in the art at the time the invention was made.

Applicant argues that the reference of Turpen does not remedy the deficiencies of Holliger, Keck and Dower, because Turpen does not disclose randomized libraries of linkers that vary in length in sequence. Therefore, the examiner has not carried the burden of a prima facie case of obviousness.

Response to Arguments

Applicant's arguments entered, 1/23/2006, have been fully considered but they are not persuasive. The examiner respectfully submits that the prior art references of

Holliger et al., Keck et al., and Dower, disclose a randomized library of linkers that differ in both length and sequence, as argued in the above response to arguments (see above paragraph 10, rejection under 35 U.S.C. § 103).

13. Claims 10, 11, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Cwirla et al.**, Proc. Natl. Acad. Sci. USA, vol. 87, pp. 6378-6382, August 1990, as applied to claims 1-4, 9, 12, 13 and 49 above, and **Turpen et al.**, WO 96/12028 (IDS filed 6/25/2002). This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

> Claims 10, 11, 14 and 15 are drawn to dual-domain nucleic acid libraries, as, for example, in claim 1, and wherein the libraries and the individual molecules of the libraries, are produced in plant cells.
> The reference of **Cwirla et al.**, is relied upon as in the above rejection under 35 USC 102/103.
> The reference of Cwirla et al., does not teach libraries and the individual molecules of the libraries, which are produced in plant cells.
> **Turpen et al.**, throughout the publication, and e.g., at p. 3, lines 7-30, pp. 4-5, bridging paragraph, teach using recombinant polynucleotides, comprised within plant viruses, in plant cells in order to produce large quantities of proteins of interest.
> It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used dual-domain nucleic acid libraries, as, for example, in claim 1, and wherein the libraries and the individual molecules of the libraries, are produced in plant cells.
> One of ordinary skill in the art would have been motivated to made and used dual-domain nucleic acid libraries in plant cells because Turpen teaches using plant viruses containing recombinant nucleic acids, in plant cells, in order to achieve high levels of gene expression.
> One of ordinary skill in the art would have had a reasonable expectation of success in producing dual-domain nucleic acid libraries in plant cells, because the genetic engineering of plant viruses, and the expression of those viruses in plant cells, were practiced in the art at the time the invention was made.

Applicant argues that the reference of Turpen does not remedy the deficiencies of Cwirla et al., because Turpen does not disclose randomized libraries of linkers that

vary in length in sequence and link a first and second domain. Therefore, the examiner has not carried the burden of a prima facie case of obviousness.

Response to Arguments

Applicant's arguments entered, 1/23/2006, have been fully considered but they are not persuasive. The examiner respectfully submits that the prior art reference of Cwirla et al., discloses a randomized library of linkers that differ in both length and sequence, and link a first and second domain, as argued in the above response to arguments (see above paragraph 9, rejection under 35 U.S.C. § 102/103).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 1-4, 9-15, and 49 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 54, 56, 60-64, 66, 67, 69, 72, 73, 76-86 of copending Application No. 09/539,382. Although the conflicting claims are not identical, they are not patentably distinct from each other

because library of dual-domain nucleic acid molecules, each of which has a first and a second domain, said domains separated and linked by a linker, wherein said linker is a member of a randomized library of linkers, wherein the linkers of the library of linkers vary in size and nucleotide sequence and consist of a "repeated pattern of degenerate repeated triplet nucleotide", and variations thereof, and nucleic acid molecules thereof, **are made obvious by**, as the species anticipates or makes obvious the genus, a polynucleotide comprising a nucleic acid sequence encoding a polypeptide epitope of a B-cell lymphoma surface immunoglobulin antigen, wherein the polypeptide is a two domain single-chain antibody that includes at least part of the VH and VL domains (claim 64), where the domains are linked by an amino acid linker (claim 66), and where the linker is a member of a randomized library of linkers that vary in size and sequence, said library being encoded by nucleic acid sequences consisting of a repeated pattern of degenerate repeated triplet nucleotides, (claim 67), and variations thereof, as claimed in copending Application No. 09/539,382.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. This rejection maintains the reasons of record as set forth in the previous Office action.

Response to Arguments

Applicant states their willingness to file a terminal disclaimer in either the instant case or in Application No. 09/539,382, depending on which case is granted first. Therefore, the instant provisional rejection is maintained.

Conclusion

15. Claims 1-4 and 9-15 stand finally rejected. Claims 49 and 50 are allowable over the prior art.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Shibuya
Examiner
Art Unit 1639

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